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REVIEW

# From Genetic Links to Personalized Therapies: Understanding Melanoma and Urological Cancer Overlap

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**Abstract**: Malignant melanoma and urological cancers originate from different tissues and organs, yet several studies highlight connections between these malignancies, including common risk factors, genetic predispositions, and immunological pathways. Evidence from recent studies suggests that a prior diagnosis of melanoma may increase the likelihood of subsequently developing renal cell carcinoma (RCC), and, conversely, patients with RCC appear to face a heightened risk of being diagnosed with melanoma. Shared factors such as a personal or family history of cancer, UV radiation exposure, smoking, and obesity have all been linked to an increased incidence of various cancer types. A major link between malignant melanoma and urological cancers is the presence of shared genetic mutations and familial cancer syndromes. Key mutations, including germline mutations in BRCA1, MITF, CDKN2A, TP53, and alterations in the PI3K/AKT pathway, significantly contribute to the risk of both types of malignancies. Personalized medicine, which tailors prevention and treatment strategies to an individual's genetic, environmental, and lifestyle factors, has significantly improved cancer care. The primary aim is to select the most effective treatment for each patient, maximizing therapeutic outcomes, reducing side effects, and minimizing the risk of drug resistance. Advances in genomics and immunology are driving the development of personalized therapies that target specific molecular pathways and immune responses common to both melanoma and urological cancers. Angiogenesis inhibitors and checkpoint inhibitors have demonstrated notable success in treating these cancers, with tumor mutational burden serving as a valuable biomarker for predicting the efficacy of immune checkpoint inhibitors.

**Keywords**: malignant melanoma; urological cancers; risk factors; shared genetic mutations; lifestyle changes; personalized treatment; tumor mutational burden; angiogenesis inhibitors; checkpoint inhibitors

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## INTRODUCTION

Cancer currently ranks as the leading cause of mortality worldwide. The growing number of cases and related deaths is primarily driven by shifts in demographic

patterns, such as population aging and growth, along with greater exposure to environmental and lifestyle-related carcinogenic factors [1].

Although malignant melanoma and urological cancers arise from different anatomical sites and tissues, multiple studies have identified links between them. These connections include overlapping risk factors, common genetic susceptibilities, and similarities in immune-related pathways involved in their development.

Gaining insight into the association between malignant melanoma and urological malignancies may contribute to the improvement of approaches for early diagnosis, risk reduction, and therapeutic management.

Although melanoma accounts for less than 2% of cancer cases globally, it remains one of the most frequently diagnosed malignancies across Europe (5th place). Survival outcomes have improved considerably in recent years, with the overall 5-year survival now approaching 93.3%. However, patients diagnosed with stage IV disease continue to face a poor prognosis, as the survival rate in advanced stages drops significantly, reaching only 29.8% [2].

Urological cancers (UC), which include kidney, bladder, prostate, testicular, penile, and urethral cancers, differ significantly in incidence, risk factors, and prognosis.

Renal cell carcinoma (RCC) represents roughly 3% of all malignant tumors diagnosed globally. The occurrence of this malignancy tends to be more frequent in industrialized nations, especially in Western societies, where lifestyle habits, environmental risk factors, and advancements in medical imaging likely play a role in higher diagnosis rates. Renal cell carcinoma represents a major public health issue due to its frequently silent evolution in early stages and the elevated risk of distant spread if not recognized in time [3]. Globally, it is estimated that more than 430,000 new cases are identified annually, underlining the increasing impact of this disease on healthcare systems. Of these cases, approximately 138,000 are reported in Europe alone, underscoring the significant prevalence of RCC across the continent. Such statistics emphasize the importance of ongoing efforts in early detection, prevention, and the development of effective treatment strategies. [4].

Urothelial carcinoma is the second most common urological malignancy in developed countries [5]. Bladder cancer (BC) accounts for 90–95% of the UC [6]. It ranks as the seventh most frequently diagnosed cancer among men globally [7].

Primary urethral carcinoma is considered a rare cancer, accounting for < 1% of all genitourinary malignancies [8].

Approximately 1.5 million new cases are reported worldwide each year. This high incidence places it as the second most commonly identified malignancy in the male population [9].

Testicular cancer (TC) accounts for 1% of adult neoplasms and 5% of urological tumors. Its incidence has risen in recent decades, particularly in industrialized countries, and continues to increase [10].

Penile cancer is a rare condition in industrialized countries, with an incidence of approximately 1 per 100,000 men in Europe and 0.5 per 100,000 in the USA [11].

The aim of this article is to evaluate the potential connections between malignant melanoma and the most common urological cancers—renal cancer, bladder cancer, and prostate cancer—from the perspectives of epidemiological factors, shared genetic mutations and molecular pathways, clinical implications, and personalized medicine.

## EPIDEMIOLOGICAL LINKS

### Environmental and Lifestyle Risk Factors for Malignant Melanoma and Urological Cancers

Advancing age, genetic predisposition, prior cancer diagnoses, radiation exposure (such as ultraviolet rays), contact with certain hazardous substances, tobacco use, alcohol intake, and excess body weight are all factors that have been linked to a higher likelihood of developing different forms of cancer.

*Ultraviolet (UV) exposure and vitamin D*

The role of ultraviolet (UV) sunlight radiation in the development of skin cancers, particularly malignant melanoma, is well-established. UVA (320–400 nm) penetrates deeper into the skin, leading to indirect DNA damage through reactive oxygen species (ROS), while UVB (280– 320 nm) directly damages DNA by inducing cyclobutane pyrimidine dimers [12]. UVB radiation can also induces mutations in genes such as TP53 and BRAF, contributing to melanomagenesis [13].

However, the association between UV exposure and RCC remains unclear, recent studies have attempted to clarify the relationship but have produced mixed results. Grasso et al. [14] found no statistically significant differences between sun exposure in patients affected by kidney cancer and controls, both during childhood and adult life. Contrary to this, Karami et al. [15] suggest that among males there is an inverse association between occupational UV exposure and renal cancer risk. Replication studies are warranted to confirm these results.

Similar to the RCC, the potential involvement of vitamin D in the development and progression of bladder cancer and upper urinary tract urothelial tumors remains underexplored. Recent epidemiological studies offer conflicting results regarding the potential link between blood levels of vitamin D and the risk of bladder cancer onset. However, several investigations suggest that individuals with a higher intake of vitamin D through diet, particularly when not accompanied by elevated calcium consumption, may have a reduced risk of developing bladder malignancies [16]. In a meta-analysis, Zhang et al. [17] concluded that Vitamin D deficiency has been linked to a heightened risk of bladder cancer. According to Gislefoss et al. [18] educed serum concentrations of 25-hydroxy vitamin D, along with obesity, may be linked to a higher risk of developing bladder cancer. The 2024 guidelines of the European Association of Urology (EAU) highlight that both insufficient and excessive levels of vitamin D have been linked to a higher likelihood of developing prostate cancer, with a particularly stronger connection observed in cases involving high-grade tumors [19,20]. Additionally, Murphy et al. demonstrated that Vitamin D deficiency was linked to higher Gleason scores and advanced tumor stages at diagnosis [21].

*Smoking*

The effect of smoking on melanoma outcome still remains an enigma [22]. In a recent study, Arafa et al. [23] found that individuals who currently smoke or have a heavy smoking history tend to exhibit a greater susceptibility to developing squamous cell carcinoma (SCC), while simultaneously displaying a lower probability of malignant melanoma. Interestingly, no significant relationship was observed between past smoking and the overall risk of skin cancer. In contrast to established risk patterns, a case-control study by Sondermeijer et al. [24] reported an inverse association between cigarette smoking and melanoma incidence in men. However, smoking remains a well-documented risk factor for various urologic malignancies.

Smokers face a significantly elevated likelihood—estimated at around 1.5 times higher—of being diagnosed with renal cell carcinoma (RCC) when compared to non-smokers [25]. Encouragingly, long-term smoking cessation has been shown to gradually diminish this elevated risk [26]. Multiple carcinogens (N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), polycyclic aromatic hydrocarbons (PAHs), Cadmium and lead (Pb), 2-naphthylamine) are absorbed through the lungs into the bloodstream and then lipophilic carcinogens may accumulate in renal tissue [27].

Cigarette smoking represents the leading modifiable contributor to bladder cancer development and is estimated to be responsible for nearly half of all diagnosed cases [28]. Low-tar cigarettes are not associated with a lower risk of developing BC. The risk associated with electronic cigarettes has not been adequately assessed. Research by Bjurlin et al. [29] revealed the presence of carcinogen-related biomarkers in the urine of individuals who use e-cigarettes, several of which have a well-established association with bladder cancer. Kispert et al. [30] recently presented a study showing that smoking is associated with increased accumulation of platelet-activating factor (PAF) and elevated expression of the PAF receptor (PAF-R), which may contribute to tumor progression and metastasis in smokers.

Current cigarette smoking has been linked to an increased risk of prostate cancer (PCa) mortality, as well as more aggressive tumor characteristics and a poorer prognosis, even after smoking cessation [31].

*Obesity*

Obesity promotes chronic inflammation, a recognized risk factor for cancer development. Inflammatory cytokines can stimulate the growth of both melanoma and renal cell carcinoma (RCC), potentially linking these two malignancies in obese patients [32].

Obesity appears to be associated with malignant melanoma, particularly in patients with a BMI >30 [2].

Several retrospective studies have shown that obesity appears to be a factor that positively influences the prognosis of patients with RCC, called the "obesity paradox" [33]. Recently, Graff and colleagues [34] provided a comprehensive review with the main purpose of disentangling the "obesity paradox" in renal cancer. The results support obesity with a BMI >35 as a risk factor for total and fatal RCC. They undermine the obesity paradox by suggesting that weight loss around diagnosis, and not low BMI itself, is associated with worse prognosis.

In the REDUCE study [35], obesity was associated with a lower risk of low-grade PCa and a higher risk of high-grade PCa.

*Occupational Exposure*

Occupational exposure to carcinogens can increase the risk of various cancers. One common risk factor for both malignant melanoma and urological cancers is exposure to polycyclic aromatic hydrocarbons.

In a 45-year follow-up study conducted across five Nordic countries, Pukkala et al. [36] found an elevated incidence of prostate cancer, malignant melanoma, non-melanoma skin cancer, and lung adenocarcinoma among firefighters, with skin absorption identified as a primary route of exposure. Similarly, individuals working in the petroleum industry are exposed to comparable risks [37].

According to the 2024 EAU Guidelines [38], occupational exposure to polycyclic aromatic hydrocarbons and other aromatic amines or hydrocarbons, mainly in the paint, dye, or petroleum industries, is the second most important risk factor for bladder cancer.

While certain studies have indicated a potential association between occupational exposure to polycyclic aromatic hydrocarbons and an increased risk of renal cancer [39,40], there is no high-quality evidence to definitively confirm this link [41].

## SHARED GENETIC MUTATIONS AND MOLECULAR PATHWAYS

Integrating molecular profiling into clinical oncology practice, particularly through mutation-focused approaches, has become essential in the evolution of precision medicine. By identifying specific genetic alterations within tumors, clinicians can better tailor immunotherapeutic interventions that modulate immune checkpoints. Therapeutic approaches that focus on modulating immune checkpoints have identified key molecular pathways, such as those involving PD-1 and its ligand, as well as CTLA-4, as critical elements in regulating immune responses against tumors. Targeting these mechanisms has opened promising prospects for the treatment of a wide range of cancers [42]. These immunotherapeutic agents have significantly reshaped treatment approaches across several types of cancers with overlapping characteristics.. Such technology was entirely unavailable before the completion of the Human Genome Project in 2001 [43]. However, current advances now enable the routine identification of relevant therapeutic mutations in many cancers, particularly in malignant melanoma and also in UC.

### Genetic Mutations in Malignant Melanoma

Melanoma exhibits one of the highest mutation frequencies among cancers [44]. The most frequent mutations are BRAF, NRAS, NF1, the TERT promoter, and CDKN2A, while KIT and TP53 mutations occur at a much lower frequency. [45].

- The BRAF mutation is the most common in malignant melanoma, occurring in 2/3 of these patients. [46]. This BRAF mutation (especially the BRAF V600 mutation) promotes cellular growth and inhibits apoptosis and is more commonly found in patients with intermittent sun exposure compared to those with chronically sun-exposed skin or unexposed skin [47].

- NRAS mutations. Among the three main proto-oncogenes of the RAS family (NRAS, KRAS, and HRAS), NRAS mutations play a key role in continuously activating pathways that lead to cell growth, proliferation, and cell cycle dysfunction. They are found in approximately 1/4 of patients with malignant melanoma, particularly in those with non-exposed skin, and are associated with aggressive clinical forms and poor prognosis [48,49].

- The neurofibromatosis type 1 (NF1) mutation leads to a loss of function in certain tumor suppressors. NF1 mutations appear to be correlated with high UV exposure, resulting in a high mutational burden [50,51].

- The TERT (telomerase reverse transcriptase) promoter mutation is a UV-induced mutation associated with poor clinical prognosis. This mutation typically occurs in the promoter region, resulting in increased expression of the gene [52].

- CDKN2A Mutation. The CDKN2A gene contributes to cellular homeostasis by limiting uncontrolled cell division through mechanisms that halt the progression of the cell cycle. Its function is essential in preventing the unchecked proliferation characteristic of tumor development. When mutations occur in this gene, normal growth regulation is disrupted, promoting tumor development. Individuals who carry CDKN2A mutations face a markedly increased risk of developing multiple primary melanomas, often at an earlier age. [53,54].

- KIT is a proto-oncogene receptor tyrosine kinase and binds to stem cell factor. By activating the KIT protein, cell growth, proliferation, survival, and migration can be affected. KIT mutations occur more commonly in areas of chronic sun damage [55].

- BAP1 Tumor Predisposition Syndrome (BAP1-TPDS) is an inherited cancer syndrome marked by germline mutations in the BRCA1-associated protein 1 (BAP1) gene [56]. The consequences include genomic instability, uncontrolled cell proliferation, and resistance to apoptosis. In the case of cutaneous melanoma, patients with germline mutations in BAP1 develop multiple atypical melanocytic lesions (dome-shaped, skin-colored to reddish papules), which are histologically distinct from conventional melanomas [57,58].

- TP53 Mutation. In human biology, the TP53 gene plays a major role in preserving genomic integrity and is often described as the "guardian of the genome." This designation stems from its crucial function in cellular defense mechanisms, particularly in detecting DNA damage and initiating appropriate responses such as cell cycle arrest, DNA repair, or apoptosis. By preventing the propagation of cells with genetic errors, TP53 serves as a key tumor suppressor and a vital component in maintaining cellular homeostasis and protecting against malignant transformation [10]. The TP53 mutation has been found in association with BRAF, NRAS, and NF1 mutations and seems to appear at a later stage in tumor development. Even though TP53 is rarely mutated in melanoma, reduced levels of p53 contribute to aggressiveness and resistance to therapy for patients with malignant melanoma [59,60].

### Genetic Mutations in Urological Cancers

There is increasing evidence that genetic susceptibility factors and familial associations may influence the incidence of UC, although their role is not as well defined as in the case of malignant melanoma.

- BAP1 Tumor Predisposition Syndrome (BAP1-TPDS) can predispose individuals not only to cutaneous and uveal melanoma but also to renal cell carcinoma (RCC) [57].

In case of cutaneous melanoma, patients with Germline mutations in BAP1 develop multiple atypical melanocytic lesions (dome-shaped, skin-colored to reddish papules), histologically distinct from conventional melanomas [58].

Kapur et al [61] in a retrospective analysis on 145 patients with primary clear cell renal cell carcinoma (ccRCC) concluded that in RCC, the clear cell subtype (ccRCC) germline mutations occur in approximately 10–15% of ccRCC. This study concluded that these patients are associated with poorer overall survival compared to those without the mutation.

Studies on the expression and prognostic role of BAP1 in prostate cancer are currently lacking. However, Steurer et al. immunohistochemically analyzed more than 17,000 prostate cancer cases, assembled on a tissue microarray over 10 10-year period, and concluded that their study shows BAP1 upregulation is associated with prostate cancer progression and aggressiveness [62].

- CDKN2A Mutation. The role of CDKN2A mutations in renal cell carcinoma is less clear. Recently, in a study, Kiatprungvech and colleagues [63] demonstrated that CDKN2A mutations may be associated with higher tumor grade and poorer prognosis in RCC, development, and sarcomatoid changes.

Deletions of CDKN2A are a molecular risk factor for tumour progression in non-muscle-invasive bladder cancers, an indicator of increased aggressiveness and worse prognosis in muscle-invasive bladder cancers [64].

In a meta-analysis investigating the involvement of CDKN2A methylation in prostate cancer, Cao et al. [65] found no strong evidence supporting a significant association between this epigenetic alteration and the onset or advancement of the disease. Nevertheless, lower levels of CDKN2A expression were correlated with poorer disease-free survival outcomes, suggesting potential prognostic relevance.

- MITF Mutation. The Microphthalmia-associated Transcription Factor (MITF) regulates genes involved in melanogenesis, melanocyte survival and proliferation, and DNA repair. The MITF-E318K variant is a heterozygous missense mutation characterized by the replacement of glutamic acid with lysine at the 318th amino acid position in the protein sequence.. Carriers have a higher risk of developing early-onset melanoma [66].

This mutation was also identified in patients with RCC, suggesting a shared genetic risk factor with melanoma. In their study, Lang et al. [67] observed that the presence of the pathogenic MITF variant in a family with bilateral and multifocal type 1 papillary renal cell carcinoma reinforces its potential role as a genetic risk factor for RCC. These findings also highlight the need to consider MITF variant screening regardless of the tumor's histological subtype.

- TP53 mutation. The role of the p53 pathway in renal cancer is underestimated. In RCC, there is a low rate of p53 mutations, which leads to poor response to conventional therapies or even therapy resistance [68].

According to findings reported by Wu et al. [69], alterations in the TP53 gene were identified in half of the individuals diagnosed with bladder cancer. It is worth noting that these genetic alterations appeared with greater frequency in tumors that had penetrated the bladder's muscular layer, as opposed to those confined to the superficial, non-muscle-invasive stages. Patients with TP53 mutations were associated with lower TP53 mRNA expression levels, more advanced tumor stages, and higher histologic grades.

- Loss of function in the VHL gene, often caused by inherited mutations, is associated with the development of von Hippel-Lindau hereditary cancer syndrome. This rare genetic condition can predispose affected individuals to various tumor types, including, in some cases, clear-cell renal cell carcinoma [70].

- Alterations in the BRCA1 and BRCA2 gene pathways have been linked to more aggressive disease phenotypes and less favorable prognoses in individuals affected by metastatic castration-resistant prostate cancer [71]. Specifically, inherited BRCA2 mutations are frequently observed in early-onset prostate cancer and are recognized as independent predictors of metastatic progression and reduced prostate cancer-specific survival [72,73]. Nyberg and colleagues [74] in a prospective cohort study confirmed the BRCA2 association with aggressive PCa. This mutation does not occur in other urological cancers or malignant melanoma.

**CLINICAL IMPLICATIONS AND PERSONALIZED MEDICINE**

Prevention is the main principle in reducing morbidity and mortality, as well as in lowering healthcare system costs.

Personalized medicine, which customizes prevention and treatment strategies based on an individual's genetic, environmental, and lifestyle factors, has greatly advanced cancer care [75].

Understanding the link between malignant melanoma and urological cancers is a key advancement toward personalized medicine.

Identifying genetic mutations and syndromes that link melanoma to urological cancers highlights the importance of genomic profiling in cancer diagnosis and treatment. The development of next-generation sequencing (NGS) technologies has made it possible to identify particular genetic alterations that may increase a person's susceptibility to various types of cancer or impact how they respond to specific therapeutic interventions [76].

**Tailoring Prevention Strategies (Table 1).**

*Reduce Ultraviolet Exposure and the Role of Vitamin D*

Excessive UV exposure is widely recognized as the leading environmental risk factor for melanoma. In people with an increased hereditary predisposition to skin cancer [77], tailored prevention approaches may involve regularly applying sunscreens that offer protection against both UVA and UVB rays, opting for clothing that minimizes sun exposure, and refraining from the use of artificial tanning devices.

In a systematic review and meta-analysis, Song et al. [78] concluded that a moderate dietary vitamin D supplement to prevent serum 25(OH)D deficiency may be beneficial for the long-term survival of melanoma patients.

A prospective study conducted by Lin et al. [58] suggested that exposure to ultraviolet radiation may be associated with a reduced incidence of prostate cancer. Additionally, research has shown that both low and excessively high levels of vitamin D may contribute to a higher likelihood of developing prostate cancer, particularly in cases involving more aggressive tumor forms [19]. Therefore, maintaining normal vitamin D levels is essential.

**Table 1:** Recommendations for lifestyle changes

| | Malignant melanoma | RCC | Bladder cancer | Prostate cancer |
|---|---|---|---|---|
| Smoking cessation | uncertain | yes | yes | yes |
| Reduce ultraviolet exposure | yes | - | - | no/increase |
| Vitamin D | moderate increase dietary | normal vitamin D levels | | |
| Obesity | uncertain | yes | yes | yes |
| Dietary antioxidants | yes | yes | yes | yes |

*Smoking Cessation in Malign Melanoma and Urological Cancers Prevention*

While the relationship between smoking and malignant melanoma remains inconclusive, tobacco use is widely recognized as a major contributor to the development of several urologic malignancies, especially bladder cancer and renal cell carcinoma. Smoking cessation programs, aided by pharmacological treatments such as nicotine replacement therapy (NRT), have proven effective in reducing the incidence or recurrence of progression of RCC [26] and bladder cancer [80]. In a network meta-analysis of 20 randomized controlled trials, Gou et al. [81] concluded that Varenicline and Bupropion increased the odds of smoking abstinence.

*Obesity and Dietary Interventions in Malignant Melanoma and Urological Cancers Prevention*

Studies that focus specifically on the link between obesity and melanoma prognosis are limited [61]. Obesity may be a risk factor for bladder cancer recurrence [83] and a higher risk of death from prostate cancer [84].

The use of dietary antioxidants has shown promising results in studies, supporting the potential role of antioxidants in the prevention of malignant melanoma related to UV exposure.

Obesity and dietary habits are well-established risk factors for prostate cancer and RCC.

Personalized weight management programs guided by genetic and metabolic profiles, and dietary recommendations, such as reducing red and processed meats and increasing intake of plant-based foods rich in antioxidants (e.g., lycopene), regular physical activity, are essential for individuals at high risk for prostate cancer and RCC [64,65].

**Screening and Surveillance**

Patients with a history of melanoma or urological cancer need careful monitoring for the potential development of additional malignancies. Routine screenings, such as skin examinations and urological assessments, can aid in early detection and improve patient outcomes. Screening for malignant melanoma is recommended for individuals with certain risk factors, including family or personal history, lifestyle or occupational predispositions, and being an older white male.

Patients with germline mutations in BAP1, CDKN2A, MITF, and other cancer-related genes may benefit from more extensive cancer screening protocols. These could include regular skin examinations for melanoma, imaging studies to detect urological cancers, and continuous monitoring for other associated malignancies.

*Skin cancer screening remains a topic of debate*.

There is an ongoing debate regarding the value of routine screening for skin cancer.

According to current assessments by major public health authorities, existing evidence is insufficient to clearly confirm or reject the benefits of regularly screening asymptomatic adults in the general population [87]. In contrast, screening is recommended for high-risk individuals by both the Australian Cancer Network [88] and the Canadian Cancer Society [89].

The group of patients at higher risk for developing skin cancer includes individuals with a personal history of skin cancer, those with light-colored skin, eyes, and hair, a high number of moles or freckles, and a history of multiple blistering sunburns during childhood [87]. In individuals at elevated risk, initial screening typically involves assessment of skin lesions using the "ABCDE" criteria, focusing on asymmetry, irregular borders, variations in color, and lesions exceeding 6 mm in diameter. Another widely used approach is the visual examination of the skin to detect pigmented lesions that appear noticeably different from the patient's other moles, a method commonly referred to as the "ugly duckling" sign [90].

The American Academy of Dermatology advises that patients diagnosed with cutaneous melanoma undergo cancer risk counseling if they present specific risk factors. These include having a family history involving three or more relatives on the same side affected by invasive melanoma or pancreatic cancer; the presence of three or more primary invasive melanomas, particularly if at least one was diagnosed before the age of 45; the occurrence of one or more melanocytic BAP1-mutated atypical intradermal tumors (MBAITs) accompanied by a family history of cancers such as mesothelioma, meningioma, or uveal melanoma; the presence of two or more MBAITs; or a broader family history that includes other forms of cancer. [91]. According to the National Comprehensive Cancer Network (NCCN), genetic testing for p16/CDKN2A mutations is advised in cases where an individual or family history includes three or more invasive cutaneous melanomas, or a combination of invasive melanoma, pancreatic cancer, and/or astrocytoma. Furthermore, individuals diagnosed with invasive cutaneous melanoma who also have a first-degree relative affected by pancreatic cancer are considered appropriate candidates for genetic evaluation. [92].

*Renal cancer screening*.

There is currently no evidence to support primary screening in the general population. The most pragmatic approach is to screen high-risk individuals or integrate this screening with other routine screening programs. This strategy improves the cost-effectiveness ratio, particularly for patients at risk of RCC [93]. Genetic assessment is advised in individuals under the age of 47, as well as in those presenting with tumors affecting both kidneys or multiple sites within the same kidney. It is also warranted for patients who have a direct or extended family history of renal cell carcinoma or relatives carrying a confirmed pathogenic genetic alteration. Additionally, testing is appropriate when histopathological characteristics raise suspicion of an inherited subtype of renal cancer [94].

*Bladder cancer screening*.

Current evaluations by major public health experts indicate a lack of sufficient high-quality evidence to clearly assess whether bladder cancer screening in asymptomatic adults provides more benefits than harms [95]. Similar recommendations are also found in the EAU Guidelines 2024 [96].

*Prostate cancer screening*.

Screening for PCa is still controversial. [97]. Prostate screening is associated with an increased diagnosis of prostate cancer (PCa), the detection of more localized disease, and fewer cases of advanced PCa. However, no PCa-specific survival benefit has been observed, and there has been no overall survival (OS) benefit [98]. Consequently, population-based screening has not been widely adopted.

According to the 2024 EAU Guidelines, PSA testing for prostate cancer screening is recommended for well-informed men at higher risk of PCa. It is generally recommended for men aged 50 and above. Earlier screening may be appropriate for those over 45 who have close relatives previously diagnosed with the disease or who belong to high-risk populations, such as individuals of African ancestry. Furthermore, men with confirmed BRCA2 mutations are advised to initiate screening starting at age 40 [99].

Hereditary genetic testing is recommended for men who have several relatives affected by prostate cancer at a relatively early age—specifically before turning 60, or in cases where a family member has died as a result of the disease. Genetic testing may also be appropriate for men who have a familial pattern of high-risk inherited mutations or a history of multiple cancer diagnoses occurring on the same side of the family [99].

**Personalized Treatment**

The goal of personalized medicine for cancer patients is to select the most effective treatment tailored to each individual, aiming for maximum efficacy, reduced side effects, a lower risk of drug resistance, and ultimately, improved overall survival. With advancements in technology, genetic testing has become increasingly accessible and is now part of routine clinical practice. [100]. Advancements in genomics and immunology are driving the development of personalized treatments that focus on specific molecular pathways and immune mechanisms common to both melanoma and urological cancers. The convergence of these genetic pathways offers promising potential for the creation of targeted therapeutic approaches.

In most cancer cases, treatment follows well-established standards that are outlined in specialized guidelines. It includes surgical therapy (nephrectomy, prostatectomy, radical cystectomy, melanoma surgery, etc.), radiotherapy, and/or hormone therapy.

In the final stages, palliative therapies are offered to patients with metastatic cancer, and these treatments can help enhance quality of life while potentially prolonging disease-free survival.

Angiogenesis inhibitors and immunotherapies have shown notable effectiveness in treating malignant melanoma and urological cancers, particularly kidney and bladder cancers. Most prostate cancers exhibit resistance to immunotherapies, particularly immune checkpoint inhibitors [101].

*Angiogenesis inhibitors.*

VEGF inhibitors function by blocking the interaction between VEGF and its receptors (VEGFRs) on endothelial cells, effectively stopping the signaling processes responsible for initiating new blood vessel formation [102]. VEGF inhibitors are primarily categorized into two groups: monoclonal antibodies, which bind directly to VEGF ligands to prevent receptor interaction, and tyrosine kinase inhibitors (TKIs), which target VEGFRs along with associated kinases to block angiogenesis signaling pathways [103,104]. These inhibitors have shown notable effectiveness in adjuvant treatment for renal cell carcinoma (RCC) and malignant melanoma, though their use is more restricted in other types of urological cancers.

Monoclonal VEGF antibodies, particularly Bevacizumab, have demonstrated effectiveness in the treatment of both renal cell carcinoma (RCC) and malignant melanoma [105,106].

Tyrosine kinase inhibitors are commonly prescribed as initial or subsequent targeted treatments for patients with kidney cancer that has progressed locally or spread to distant sites [107,108]. Initial treatment with sunitinib alone has demonstrated significant benefits by delaying disease progression and enhancing the overall tumor response. Some tyrosine kinase inhibitors, such as pazopanib, have shown similar effectiveness to sunitinib when used in the initial treatment of patients with metastatic kidney cancer [109]. Certain agents, including cabozantinib, have shown clinical benefit in patients with advanced clear-cell renal cell carcinoma that no longer responds to therapies targeting the VEGF receptor pathway. This option is particularly relevant for individuals who have not yet received immune checkpoint inhibitors and who have previously undergone one or two systemic treatment regimens [110].

For patients with malignant melanoma, sunitinib may show efficacy, particularly in those with KIT mutations [111].

*Checkpoint inhibitors*

Immunotherapeutic strategies—especially those directed at modulating checkpoint pathways—have shown significant efficacy in the treatment of various cancers. A prominent category within these therapies includes drugs designed to block the binding between PD-L1 and its associated receptor, PD-1, both of which are crucial in helping tumors evade immune surveillance. Interrupting this interaction enables the reactivation of T cells, thereby strengthening the immune system’s capacity to detect and destroy malignant cells.

Tumor mutational burden (TMB) serves as an essential biomarker for predicting immunotherapy outcomes, representing the total count of somatic mutations within a tumor's DNA. Although tumor mutational burden (TMB) does not appear to impact the success of treatments aimed at inhibiting angiogenesis, it is considered an important biomarker in forecasting patient responsiveness to immunotherapeutic strategies. These treatments work by altering specific immune checkpoints involved in immune regulation, including pathways mediated by proteins like PD-1, PD-L1, and CTLA-4 [112]. Tumors with a high mutational burden typically generate a higher quantity of neoantigens (abnormal proteins created by genetic mutations). This abundance of neoantigens improves the chances of immune system recognition and response, thereby boosting the effectiveness of immunotherapy [113]. Cancers such as melanoma, lung cancer, and urothelial cancers often have a high tumor mutational burden (TMB), while prostate and breast cancers typically show lower TMB [69]. Tumors with high TMB tend to express a wider array of neoantigens, making them more prone to immune system recognition and response, particularly when treated with checkpoint inhibitors. As a result, immunotherapy is generally more effective in cancers with elevated TMB [114,115].

Both malignant melanoma and RCC are highly immunogenic tumors, meaning they can provoke an immune response. The strong immunogenic nature of both cancer types has contributed to their responsiveness to immunotherapeutic approaches, especially those involving checkpoint blockade with agents targeting PD-1 and CTLA-4. However, the application of PD-L1 inhibitors in the treatment of renal cell carcinoma remains relatively restricted [116].

After the introduction of ipilimumab in 2011 for the systemic treatment of melanoma, immunotherapy has made significant strides in treating both resectable and unresectable melanoma [117]. The CheckMate 037 [118,119]and CheckMate 066 trials established nivolumab's efficacy in patients with metastatic melanoma. Additionally, the KEYNOTE-006 trial, which compared pembrolizumab and ipilimumab for advanced melanoma, showed pembrolizumab's superiority in terms of the 2-year overall survival rate [120].

In the 2023 ASCO Guideline Update on Systemic Therapy for Melanoma, checkpoint inhibitors are positioned as the primary treatment choice for malignant melanoma. They are recommended for neoadjuvant therapy (in resected stage III B-IV melanoma), as adjuvant therapy (for resected stage II B or higher), and for unresectable melanoma. For patients with unresectable or metastatic cutaneous

melanoma, or resected stage IV melanoma, the combination of ipilimumab and nivolumab serves as one of the primary treatment options [121].

In selected cases of metastatic kidney cancer, monotherapy with an immune checkpoint inhibitor, such as pembrolizumab, can represent a suitable therapeutic choice, particularly when combination regimens are not indicated or tolerated. However, in metastatic patients whose disease is categorized as intermediate or poor risk and who are suitable candidates for immunotherapy, current clinical guidelines tend to favor starting with a dual-agent immunotherapeutic regimen as the initial line of systemic treatment [122]. Currently, five immunotherapy-based combination treatments have received approval for clinical use. These include the pairing of ipilimumab with nivolumab, pembrolizumab with axitinib, as well as other therapeutic duos such as nivolumab combined with cabozantinib, avelumab administered alongside axitinib, and pembrolizumab used in conjunction with Lenvatinib [123]. Among these, the ipilimumab and nivolumab combination is specifically approved for intermediate- and poor-risk mRCC patients [124].

Despite their efficacy, these agents also cause immune-related adverse effects that may be life-threatening if not detected and controlled appropriately [125].

Targeting the PD-1/PD-L1 immune checkpoint pathway has demonstrated significant therapeutic benefits in patients with advanced or inoperable bladder cancer, including those with metastatic disease. Nivolumab has received FDA approval as adjuvant therapy in individuals with urothelial carcinoma who face an elevated risk of disease recurrence after undergoing surgery. Additionally, the PD-1 inhibitor pembrolizumab was authorized for use in patients whose condition has worsened despite prior treatment with platinum-based chemotherapy, a decision supported by findings from the phase III clinical study known as KEYNOTE-045 [126].

For prostate cancer, the use of angiogenesis and checkpoint inhibitors in therapeutic strategies is limited. Currently, pembrolizumab is the only FDA-approved treatment option, although it has not been approved by the EMA. [127].

Beyond the therapies previously mentioned, each of these pathologies benefits from specific treatments targeting different types of genetic mutations and molecular pathways.

For malignant melanoma with BRAF gene mutations (V600E/K), treatment combinations such as dabrafenib with trametinib (or encorafenib with binimetinib) are indicated [128,129].

In prostate cancer, besides androgen receptor pathway inhibitors, non-hormonal, non-cytotoxic treatments like poly-ADP ribose polymerase inhibitors (PARPi) have emerged, specifically designed to target cancer cells harboring BRCA mutations [130]. While no AKT inhibitors are currently approved, the investigational drug ipatasertib has demonstrated significant activity in clinical trials when combined with abiraterone acetate in patients with loss of the tumor suppressor protein PTEN, as confirmed by immunohistochemistry [131].

## CONCLUSION

The link between malignant melanoma and urological cancers is underpinned by common epidemiological factors and genetic mutations, establishing a foundation for progress in personalized medicine. As understanding of the shared molecular pathways in these cancers expands, opportunities for tailored prevention strategies, screening practices, and individualized treatments become increasingly apparent. Identifying genetic predispositions—such as BAP1 and CDKN2A mutations—early on, along with employing targeted therapies and immunotherapies, is expected to meaningfully enhance patient care in the near future.

Personalized medicine holds great promise for patients with elevated risks of both melanoma and urological cancers. By leveraging genomic profiling alongside advancements in immunotherapy and targeted therapies, more tailored and effective treatment options become possible, enhancing patient outcomes. However, ongoing research and clinical trials are essential to fully understand the effects of shared genetic mutations and molecular pathways and to establish comprehensive, individualized treatment protocols. Further refinement in treatment sequencing approaches will also be necessary to optimize care for these patients.

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***Authors' contribution***

*DPH contributed to the manuscript's conceptualization, methodology, discussion, supervision, and writing. MAB contributed to the manuscript's editing, data curation, and writing. NM contributed to the editing and data curation of the manuscript. OSC contributed to the conceptualization, discussion, and supervision of the manuscript. MDV contributed to the manuscript's conceptualization, editing, and data curation. CT contributed to the discussion, data curation, and writing of the manuscript. IA contributed to the methodology, review, and editing of the manuscript. BOF contributed to the conceptualization, discussion, review, and supervision of the manuscript. VMG contributed to the editing, data curation, and writing of the manuscript. OKIM contributed to the conceptualization, discussion, and supervision of the manuscript. CTM contributed to the conceptualization, methodology, investigation, discussion, review, editing, supervision, data curation, and writing of the manuscript.. All authors have read and agreed to the published version of the manuscript.*

***Ethics approval and consent to participate***

*The study was conducted under the Declaration of Helsinki. The research was conducted under ethical guidelines and regulations, ensuring compliance with all necessary protocols.*

***Patient consent for publication***

*Written informed consent has been obtained from the patient to publish this paper.*

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